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(73)专利权人 沈阳中化农药化工研发有限公司

地址 110021 辽宁省沈阳市铁西区沈辽东
路8-1号

(72)发明人 于海波 王学玲 赵贵民 黄耀师
徐凤波 杨辉斌 李斌

(74)专利代理机构 沈阳科苑专利商标代理有限公司 21002

代理人 李颖 何薇

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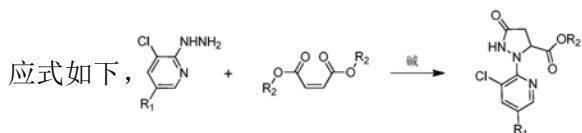
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(54)发明名称

吡啶基吡唑烷酮羧酸类化合物的制备方法

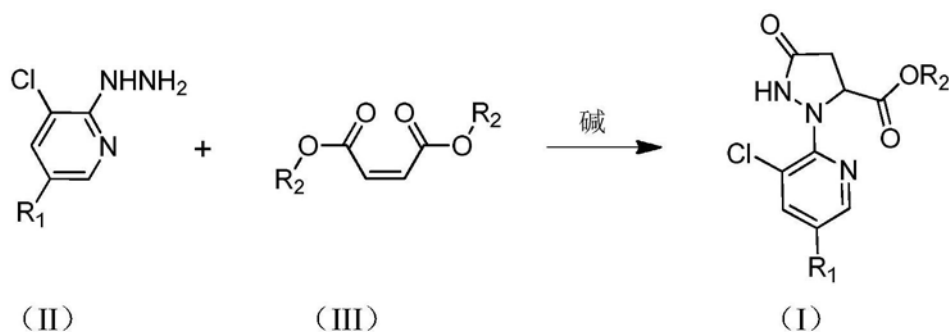
(57)摘要

本发明属于有机合成领域,具体地涉及一种吡啶基吡唑烷酮羧酸酯类化合物的制备方法。反



式中各基团定义见说明书。本发明提供了一种制备苯甲酰胺类杀虫剂关键中间体吡啶基吡唑烷酮羧酸酯类化合物的方法,采用本发明的方法提高了产物的收率,减少了能源消耗,更易于工业化生产。

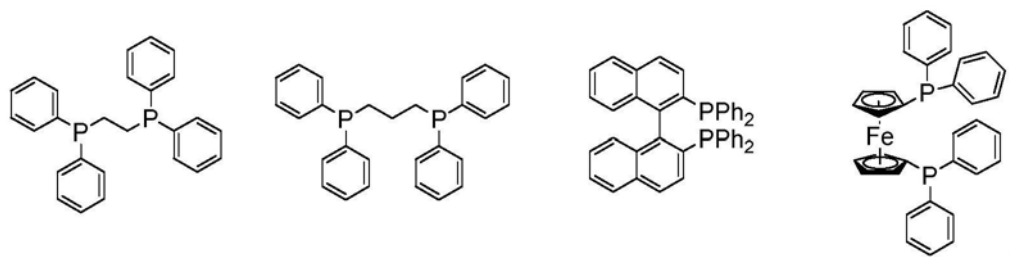
1. 一种吡啶基吡唑烷酮羧酸酯类化合物的制备方法,其特征在于:
反应式如下:



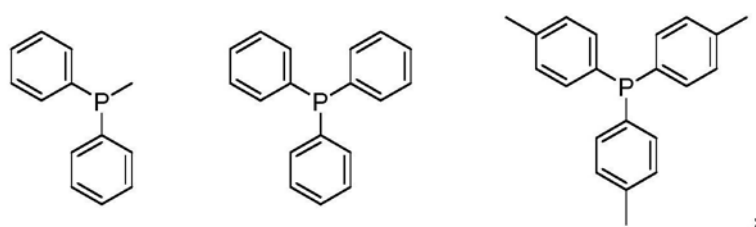
式中:R₁选自H或Cl;R₂选自甲C₁-C₆烷基、C₂-C₄烯基、C₂-C₄炔基、C₃-C₆环烷基、卤素或C₁-C₄烷基取代的苄基;

胍基吡啶(II)在碱性条件下、在适宜的溶剂中,通过催化剂的作用与马来酸二酯(III),在0℃至所用溶剂的沸点范围内反应制得吡啶基吡唑烷酮羧酸酯类化合物(I),

其中,胍基吡啶、碱、马来酸二酯和催化剂的摩尔配比为1:1-2:1-5:0.00001-0.01;催化剂选自:Cu(L1)Cl, Cu(L1)Br, Cu(L1)I, Cu(L2)₂Cl, Cu(L2)₂Br, Cu(L2)₂I; Ni(L1)Cl₂, Ni(L1)Br₂, Ni(L1)I₂, Ni(L2)₂Cl₂, Ni(L2)₂Br₂, Ni(L2)₂I₂, 其中L1选自:



L2选自:



所述适宜的溶剂选自甲苯,氯苯,羧酸酯类,烷基醇类,醚类或极性非质子性溶剂;

所述碱选自碱金属的氢化物、碱金属的氨化物或烷基醇化物;

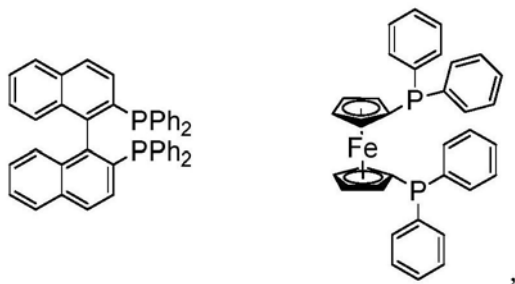
所述碱金属的氢化物为氢化锂、氢化钠、氢化钾,碱金属的氨化物为氨基锂、氨基钠、氨基钾,烷基醇化物为甲醇钠,乙醇钠,丙醇钠,丁醇钠,戊醇钠,异丙醇钠,异丁醇钠,另丁醇钠,叔丁醇钠,甲醇钾、乙醇钾,丙醇钾或叔丁醇钾;碱金属选自锂,钠或钾;

所述羧酸酯类为乙酸酯,富马酸二酯或马来酸二酯;烷基醇类为甲醇,乙醇,丙醇,丁醇,戊醇,异丙醇,异丁醇,另丁醇或叔丁醇;醚类为四氢呋喃,2-甲基四氢呋喃,二氧六环;极性非质子性溶剂为乙腈,N,N-二甲基甲酰胺,N,N-二甲基乙酰胺或二甲基亚砷。

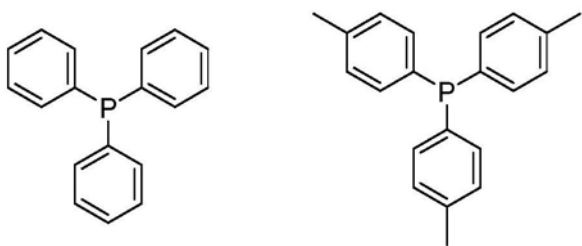
2. 按权利要求1所述的吡啶基吡唑烷酮羧酸酯类化合物的制备方法,其特征在于:胍基吡啶(II)在碱性条件下、在适宜的溶剂中,通过催化剂的作用与马来酸二酯(III),在20-50℃下反应制得吡啶基吡唑烷酮羧酸酯类化合物(I),

其中, 肼基吡啶、碱、马来酸二酯和催化剂的摩尔配比为1:1.2-1.5:1.5-2:0.0001-0.001; 催化剂选自Cu (L1) Br, Cu (L1) I, Cu (L2) ₂Br或Cu (L2) ₂I; 其中

L1选自:

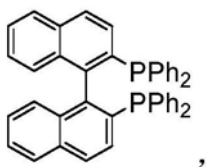


L2选自:

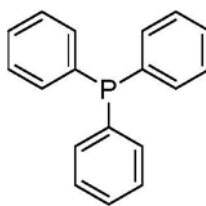


3. 按权利要求2所述的吡啶基吡唑烷酮羧酸酯类化合物的制备方法, 其特征在于: 所述催化剂选自Cu (L1) I或Cu (L2) ₂I, 其中

L1选自:



L2选自:



4. 按权利要求1所述的吡啶基吡唑烷酮羧酸酯类化合物的制备方法, 其特征在于: 所述碱选自甲醇钠, 乙醇钠, 丙醇钠, 丁醇钠, 戊醇钠, 异丙醇钠, 异丁醇钠, 另丁醇钠或叔丁醇钠; 所述适宜的溶剂选自甲醇, 乙醇, 丙醇, 丁醇, 戊醇, 异丙醇, 异丁醇, 另丁醇或叔丁醇。

5. 按权利要求4所述的吡啶基吡唑烷酮羧酸酯类化合物的制备方法, 其特征在于: 所述碱选自乙醇钠, 所述适宜的溶剂选自乙醇。

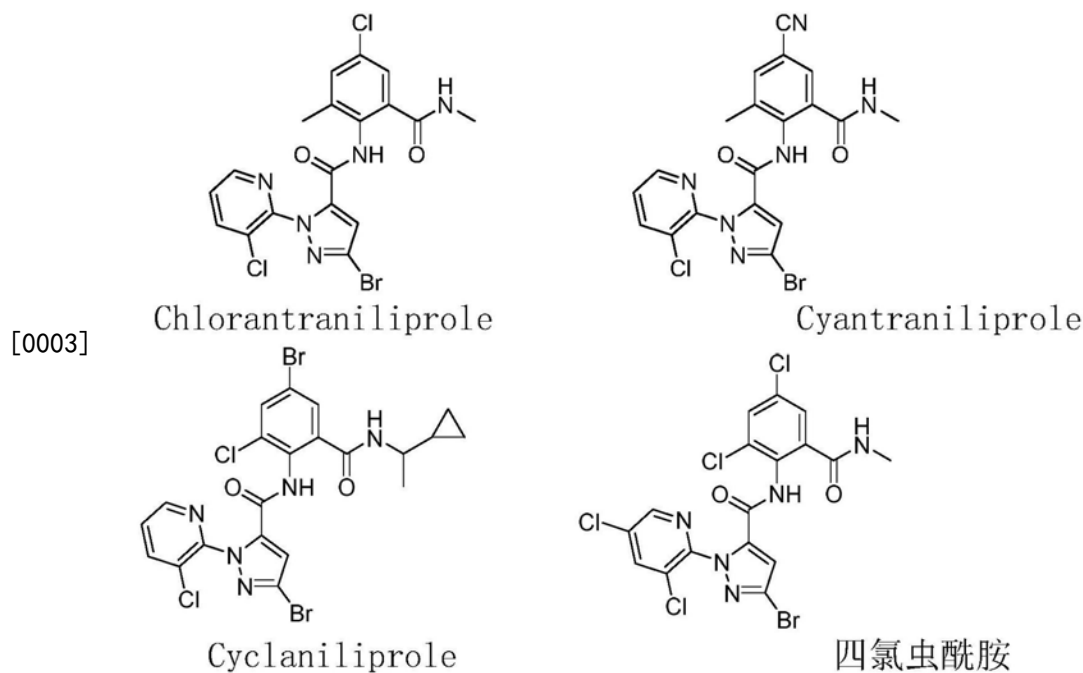
吡啶基吡唑烷酮羧酸类化合物的制备方法

技术领域

[0001] 本发明属于有机合成领域,具体地涉及一种吡啶基吡唑烷酮羧酸酯类化合物的制备方法。

背景技术

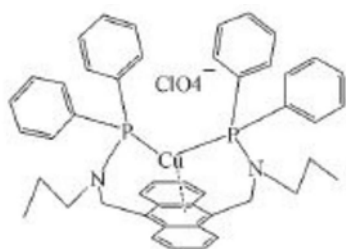
[0002] 苯甲酰胺类化合物是一类高效、安全的新型杀虫剂。其中3-溴-N-(2-甲基-4-氯-6-(甲氨酰基)苯基)-1-(3-氯-2-吡啶基)-1H-吡唑-5-甲酰胺(通用名为chlorantraniliprole)、3-溴-N-(2-甲基-4-氰基-6-(甲氨酰基)苯基)-1-(3-氯-2-吡啶基)-1H-吡唑-5-甲酰胺(通用名为cyantraniliprole)具有高的杀虫活性,杜邦公司已开发为杀虫剂。石原产业株式会社正在开发的双酰胺类化合物3-溴-N-(2-氯-4-溴-6-((1-环丙基乙基)酰基)苯基)-1-(3-氯-2-吡啶基)-1H-吡唑-5-甲酰胺的(通用名为cyclaniliprole),具有广谱的杀虫活性。沈阳化工研究院发现了具有高杀虫活性的3-溴-N-(2,4-二氯-6-(甲氨酰基)苯基)-1-(3,5-二氯-2-吡啶基)-1H-吡唑-5-甲酰胺,也已经开发为杀虫剂,通用名为四氯虫酰胺。



[0004] 1-(3-氯吡啶-2-基)-3-吡唑烷酮-5-羧酸酯是合成chlorantraniliprole、cyantraniliprole、cyclaniliprole的共用关键中间体,W02004011453中公开了1-(3-氯吡啶-2-基)-3-吡唑烷酮-5-羧酸酯的合成,由胍基吡啶与马来酸二酯在回流温度下反应制得,反应收率仅为55%。

[0005] 南开大学徐凤波等报道了使用结构复杂的含蒽环的双胺配合物A做为催化剂合成1-(3-氯吡啶-2-基)-3-吡唑烷酮-5-羧酸乙酯的方法(参考文献:农药研究与应用.14(2), 14-15,2009),收率为70%。催化剂具体结构如下:

[0006]



化合物 A

[0007] 一直以来,技术人员致力于不断研究开发新的、更为先进合理的吡啶基吡唑烷酮羧酸酯类化合物制备方法,以期获得质量更优、价格更低的苯甲酰胺类杀虫剂。

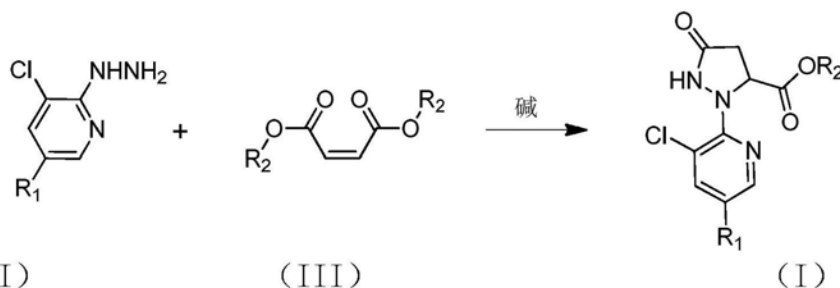
发明内容

[0008] 本发明的目的在于提供一种更为简便、更加高效地吡啶基吡唑烷酮羧酸酯类化合物的制备方法。

[0009] 为实现上述目的,本发明采用的技术方案为:

[0010] 一种吡啶基吡唑烷酮羧酸酯类化合物的制备方法,反应式如下:

[0011]

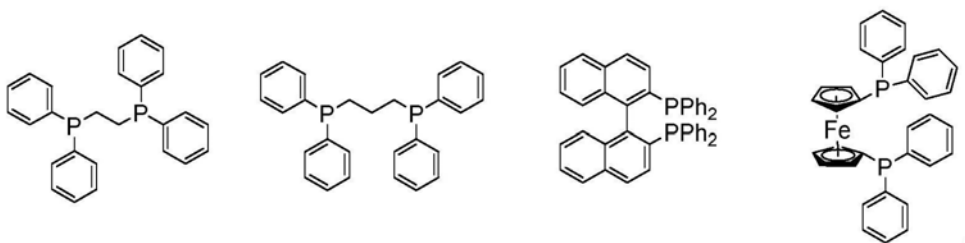


[0012] 式中: R_1 选自H或Cl; R_2 选自甲 C_1 - C_6 烷基、 C_2 - C_4 烯基、 C_2 - C_4 炔基、 C_3 - C_6 环烷基、卤素或 C_1 - C_4 烷基取代的苄基;

[0013] 胂基吡啶(II)在碱性条件下、在适宜的溶剂中,通过催化剂的作用与马来酸二酯(III),在 0°C 至所用溶剂的沸点范围内反应制得吡啶基吡唑烷酮羧酸酯类化合物(I),

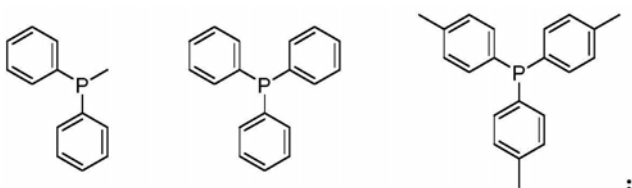
[0014] 其中,胂基吡啶、碱、马来酸二酯和催化剂的摩尔配比为1:1-2:1-5:0.00001-0.01;催化剂选自: $\text{Cu}(\text{L1})\text{Cl}$, $\text{Cu}(\text{L1})\text{Br}$, $\text{Cu}(\text{L1})\text{I}$, $\text{Cu}(\text{L2})_2\text{Cl}$, $\text{Cu}(\text{L2})_2\text{Br}$, $\text{Cu}(\text{L2})_2\text{I}$; $\text{Ni}(\text{L1})\text{Cl}_2$, $\text{Ni}(\text{L1})\text{Br}_2$, $\text{Ni}(\text{L1})\text{I}_2$, $\text{Ni}(\text{L2})_2\text{Cl}_2$, $\text{Ni}(\text{L2})_2\text{Br}_2$, $\text{Ni}(\text{L2})_2\text{I}_2$,其中L1选自:

[0015]



[0016] L2选自:

[0017]



[0018] 所述适宜的溶剂选自甲苯,氯苯,羧酸酯类,烷基醇类,醚类或极性非质子性溶剂;

[0019] 所述碱选自碱金属的氢化物、碱金属的氨化物或烷基醇化物。

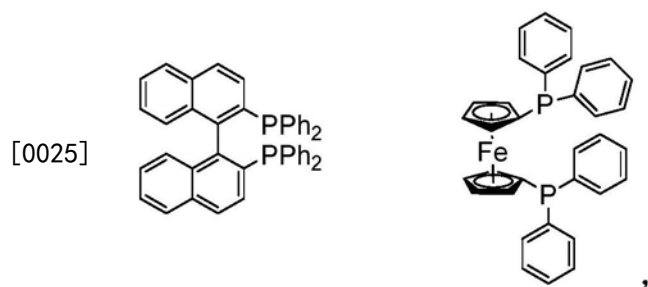
[0020] 所述碱金属的氢化物为氢化锂、氢化钠、氢化钾,碱金属的氨化物为氨基锂、氨基钠、氨基钾,烷基醇化物为甲醇钠,乙醇钠,丙醇钠,丁醇钠,戊醇钠,异丙醇钠,异丁醇钠,另丁醇钠,叔丁醇钠,甲醇钾、乙醇钾,丙醇钾或叔丁醇钾;碱金属选自锂,钠或钾;

[0021] 所述羧酸酯类为乙酸酯,富马酸二酯或马来酸二酯;烷基醇类为甲醇,乙醇,丙醇,丁醇,戊醇,异丙醇,异丁醇,另丁醇或叔丁醇;醚类为四氢呋喃,2-甲基四氢呋喃,二氧六环;极性非质子性溶剂为乙腈,N,N-二甲基甲酰胺,N,N-二甲基乙酰胺或二甲基亚砷。

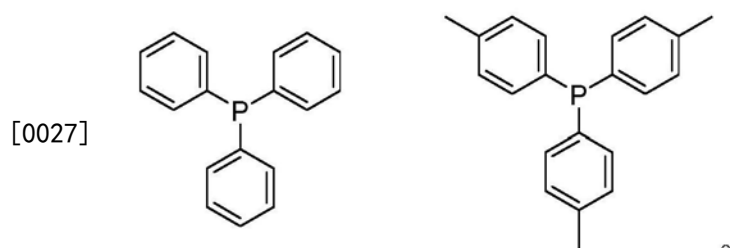
[0022] 优选,胍基吡啶(II)在碱性条件下、在适宜的溶剂中,通过催化剂的作用与马来酸二酯(III),在20-50℃下反应制得吡啶基吡唑烷酮羧酸酯类化合物(I),

[0023] 其中,胍基吡啶、碱、马来酸二酯和催化剂的摩尔配比为1:1.2-1.5:1.5-2:0.0001-0.001;催化剂选自Cu(L1)Br,Cu(L1)I,Cu(L2)₂Br或Cu(L2)₂I;其中

[0024] L1选自:

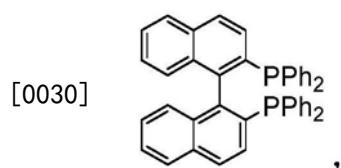


[0026] L2选自:

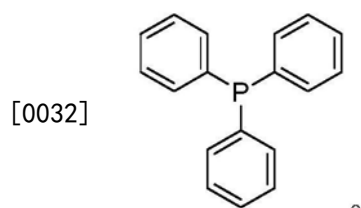


[0028] 进一步优选,所述催化剂选自Cu(L1)I或Cu(L2)₂I,其中

[0029] L1选自:



[0031] L2选自:



[0033] 所述碱选自甲醇钠,乙醇钠,丙醇钠,丁醇钠,戊醇钠,异丙醇钠,异丁醇钠,另丁醇

钠或叔丁醇钠;所述适宜的溶剂选自甲醇,乙醇,丙醇,丁醇,戊醇,异丙醇,异丁醇,另丁醇或叔丁醇。

[0034] 所述碱选自乙醇钠。所述适宜的溶剂选自乙醇。

[0035] 上面给出的合成方法及各通式化合物中基团的定义中,汇集所用术语一般定义如下:

[0036] 烷基是指直链或支链形式,例如甲基、乙基、正丙基、异丙基、正丁基、异丁基、仲丁基、特丁基、正戊基、异戊基等基团。环烷基是指包括环状链形式,例如环丙基、环丁基、环戊基、环己基、甲基环丙基、环丙基环丙基等基团。烯基是指直链或支链烯基,如1-丙烯基、2-丙烯基和不同的丁烯基等。炔基是指直链或支链炔基,如1-丙炔基、2-丙炔基和不同的丁炔基等。卤素是指氟、氯、溴、碘。

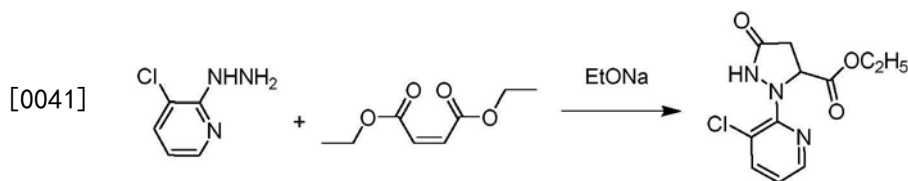
[0037] 本发明所具有有点:本发明采用结构简单的不含氮的苯基膦化合物作为催化吡啶基吡唑烷酮羧酸酯的合成的催化剂,可以大大提高反应的收率,从而完成了本发明。同时,本发明反应可在较低温度下进行,使反应的安全性大大提高。另外,本发明的催化剂还存在合成简单易行、价格低廉的优势,只需金属盐和苯基膦在乙醇中反应即可制得。因此,本发明的催化剂更易于在工业化生产中的应用。

具体实施方式

[0038] 下面通过列举实施例来对本发明进行更详细的说明吡啶基吡唑烷酮羧酸酯类化合物制备方法,但并不意味着限制本发明。

[0039] 实施例1

[0040] 1-(3-氯吡啶-2-基)-3-吡唑烷酮-5-羧酸乙酯的合成



[0042] 在2000毫升反应瓶内加入1000毫升无水乙醇和乙醇钠(65.7克,0.966摩尔),3-氯-2-肼基吡啶(101.04克,98%,0.69摩尔),再加入催化剂Cu(PPh₃)₂I(0.15克,0.00021摩尔)(双三苯基膦碘化亚铜,合成方法参加:Chemistry-A European Journal,16(39),11822-11826,2010)混合物加热至40℃,滴加马来酸二乙酯(145.7克,0.83摩尔)。保持此温度4h,而后将反应混合物用冰乙酸(60克)中和。混合物用1000毫升水稀释,冷至室温,有固体析出。过滤收集固体,用3×150毫升40%的乙醇水溶液洗涤。干燥后得1-(3-氯-2-吡啶基)-3-吡唑烷酮-5-甲酸乙酯橙色固体149.91克,外标法定量分析其含量为98%,收率79%。¹H NMR(300MHz,DMSO):8.289-8.269(q,1H),7.956-7.190(q,1H),7.231-7.190(q,1H),4.862-4.816(q,1H),4.236-4.165(q,2H),2.967-2.879(q,1H),2.396-2.336(q,1H),1.250-1.202(t,3H)。

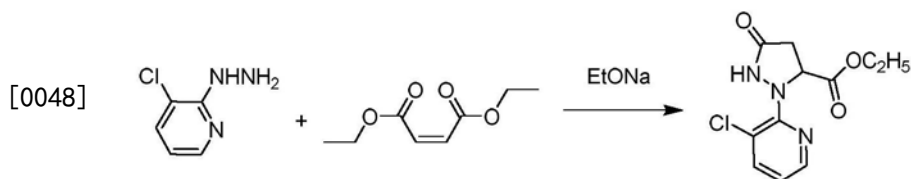
[0043] 催化剂的合成方法如下:

[0044] 在2000毫升反应瓶内依次加入1000毫升无水乙醇、三苯基膦(500克,1.9mol)、CuI(181克,0.95mol),升温至80℃反应1h后,自然降温至室温,过滤,干燥,得产品644.9克,收率95%。

[0045] 下述其它催化剂选择适宜的原料可按照此方式制备获得。

[0046] 实施例2

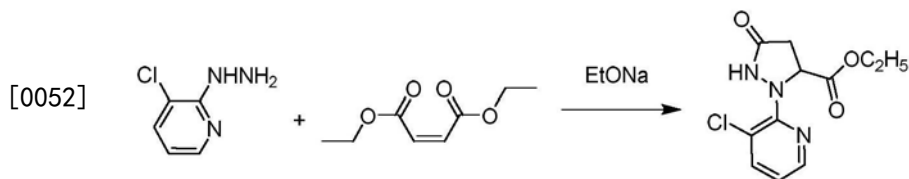
[0047] 1-(3-氯吡啶-2-基)-3-吡唑烷酮-5-羧酸乙酯的合成



[0049] 在1000毫升反应瓶内加入300毫升无水乙醇和乙醇钠(16.97克,0.249摩尔),3-氯-2-肼基吡啶(30.75克,98%,0.21摩尔),再加入催化剂Cu(binap)I(0.017克,0.000021摩尔)(2,2'-双-(二苯膦基)-1,1'-联萘简称binap,合成方法参加:Chemistry-A European Journal,16(39),11822-11826,2010)混合物加热至30℃,滴加马来酸二乙酯(44.23克,0.252摩尔)。保持此温度4h,而后将反应混合物用冰乙酸(15克,)中和。混合物用300毫升水稀释,冷至室温,有固体析出。过滤收集固体,用3×50毫升40%的乙醇水溶液洗涤。干燥后得1-(3-氯-2-吡啶基)-3-吡唑烷酮-5-甲酸乙酯橙色固体47.06克,外标法定量分析其含量为95%,收率79%。

[0050] 实施例3

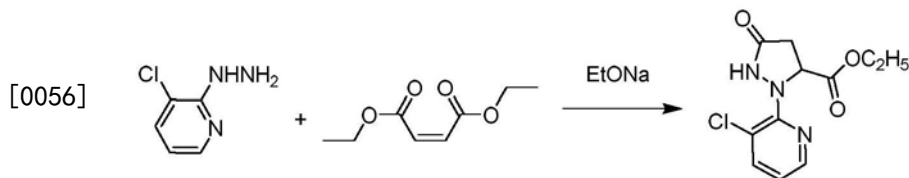
[0051] 1-(3-氯吡啶-2-基)-3-吡唑烷酮-5-羧酸乙酯的合成



[0053] 在1000毫升反应瓶内加入300毫升无水乙醇和乙醇钠(16.97克,0.249摩尔),3-氯-2-肼基吡啶(30.75克,98%,0.21摩尔),再加入催化剂Cu(PPh₃)₂Br(0.042克,0.000063摩尔)(双三苯基膦溴化亚铜,合成方法参加:Chemistry-A European Journal,16(39),11822-11826,2010),混合物加热至35℃,滴加马来酸二乙酯(44.23克,0.252摩尔)。保持此温度4h,而后将反应混合物用冰乙酸(15克)中和。混合物用300毫升水稀释,冷至室温,有固体析出。过滤收集固体,用3×50毫升40%的乙醇水溶液洗涤。干燥后得1-(3-氯-2-吡啶基)-3-吡唑烷酮-5-甲酸乙酯橙色固体45.98克,外标法定量分析其含量为96%,收率78%。

[0054] 实施例4

[0055] 1-(3-氯吡啶-2-基)-3-吡唑烷酮-5-羧酸乙酯的合成



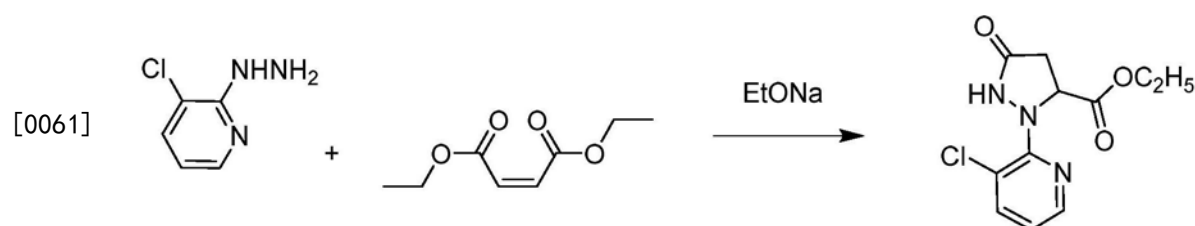
[0057] 在1000毫升反应瓶内加入300毫升无水乙醇和乙醇钠(16.97克,0.249摩尔),3-氯-2-肼基吡啶(30.75克,98%,0.21摩尔),再加入催化剂Ni(PPh₃)₂Br₂(0.047克,0.000063摩尔)(双三苯基膦二溴化镍合成方法参加:Appl.Organometal.Chem.,23,455-459,2009),混合物加热至45℃,滴加马来酸二乙酯(44.23克,0.252摩尔)。保持此温度4h,而后将反应

混合物用冰乙酸(15克)中和。混合物用300毫升水稀释,冷至室温,有固体析出。过滤收集固体,用3×50毫升40%的乙醇水溶液洗涤。干燥后得1-(3-氯-2-吡啶基)-3-吡唑烷酮-5-甲酸乙酯橙色固体45.98克,外标法定量分析其含量为96%,收率78%。

[0058] 按照实施例1中的方法,使用催化剂 $\text{Cu}(\text{PPh}_3)_2\text{I}$ (双三苯基膦碘化亚铜)可以高收率的制得1-(3,5-二氯吡啶-2-基)-3-吡唑烷酮-5-羧酸乙酯。 ^1H NMR (300MHz, CDCl_3): 8.146 (q, 1H), 7.658 (q, 1H), 5.073 (dd, 1H), 4.241 (q, 2H), 3.029 (dd, 1H), 2.721 (dd, 1H), 1.258 (t, 3H)。

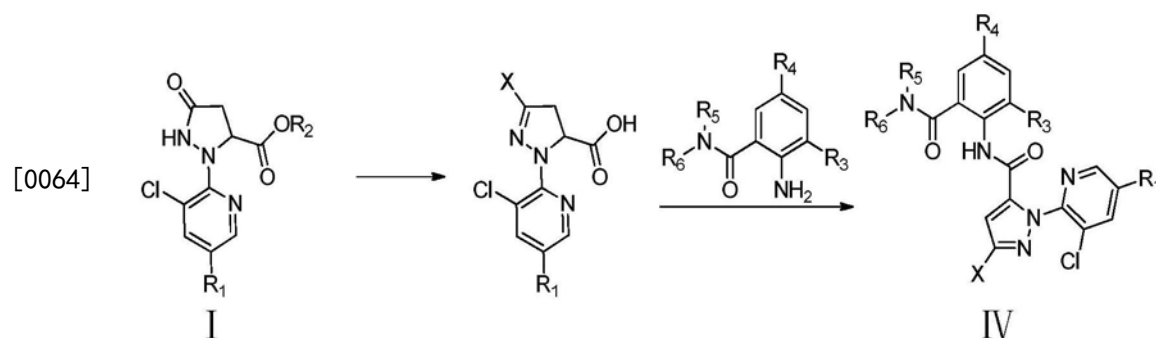
[0059] 对照实施例

[0060] 按照南开大学公开方法(参考文献:农药研究与应用.14(2),14-15,2009)合成了1-(3-氯吡啶-2-基)-3-吡唑烷酮-5-羧酸乙酯。



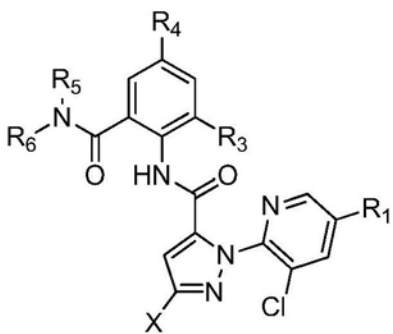
[0062] 在1000毫升反应瓶内加入300毫升无水乙醇和钠(5.22克,0.227摩尔),搅拌至无气泡产生,加入3-氯-2-肼基吡啶(30.00克,0.205摩尔),混合物加热至回流5min,再加入催化剂A 0.003克,滴加马来酸二乙酯(36.00克,0.209摩尔)。保持回流30min,而后将反应混合物冷却至65℃用冰乙酸(25.2克)中和。混合物用300毫升水稀释,冷至室温,有固体析出。过滤收集固体,用3×50毫升40%的乙醇水溶液洗涤。干燥后得1-(3-氯-2-吡啶基)-3-吡唑烷酮-5-甲酸乙酯,橙色固体45.2克,归一含量96%,外标法定量分析其含量为85.4%,收率70%。

[0063] 本发明得到的吡啶基吡唑烷酮羧酸酯进一步经卤化、水解得到3-卤代-1-吡啶基吡唑-5-羧酸。吡唑羧酸和取代苯胺反应制得通式IV所示的苯甲酰胺类化合物。表1列出部分通式(IV)化合物的结构。



[0065] 表1. 部分通式(IV)化合物的结构

[0066]



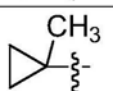
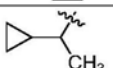
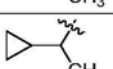
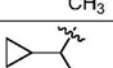
[0067]

化合物	R ₁	R ₃	R ₄	R ₅	R ₆	X
1	H	CH ₃	Cl	H	H	Br
2	H	Cl	Cl	H	H	Br
3	H	CH ₃	Br	H	H	Br
4	H	Cl	Br	H	H	Br
5	Cl	CH ₃	F	H	H	Br
6	Cl	Cl	F	H	H	Br
7	Cl	CH ₃	Cl	H	H	Br
8	Cl	Cl	Cl	H	H	Br
9	Cl	CH ₃	Br	H	H	Br
10	Cl	Cl	Br	H	H	Br
11	H	CH ₃	F	H	CH ₃	Br
12	H	Cl	F	H	CH ₃	Br
13	H	CH ₃	Cl	H	CH ₃	Br
14	H	F	Cl	H	CH ₃	Br
15	H	Cl	Cl	H	CH ₃	Br
16	H	Br	Cl	H	CH ₃	Br
17	H	CN	Cl	H	CH ₃	Br
18	H	CH ₃	Br	H	CH ₃	Br
19	H	F	Br	H	CH ₃	Br
20	H	Cl	Br	H	CH ₃	Br
21	H	Br	Br	H	CH ₃	Br
22	H	CN	Br	H	CH ₃	Br
23	H	CH ₃	CN	H	CH ₃	Br
24	H	F	CN	H	CH ₃	Br
25	H	Cl	CN	H	CH ₃	Br
26	H	CN	CN	H	CH ₃	Br
27	H	Br	CN	H	CH ₃	Br
28	Cl	CH ₃	F	H	CH ₃	Br
29	Cl	Cl	F	H	CH ₃	Br
30	Cl	CH ₃	Cl	H	CH ₃	Br
31	Cl	F	Cl	H	CH ₃	Br
32	Cl	Cl	Cl	H	CH ₃	Br

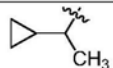
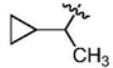
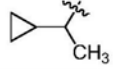
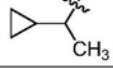
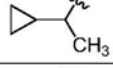
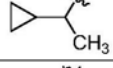
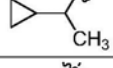
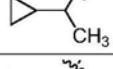
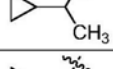
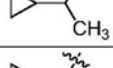
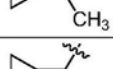
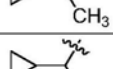
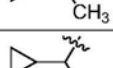
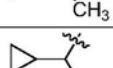
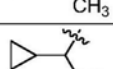
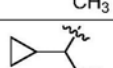
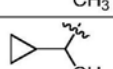
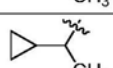
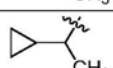
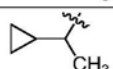
[0068]

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36	Cl	F	Br	H	CH ₃	Br
37	Cl	Cl	Br	H	CH ₃	Br
38	Cl	Br	Br	H	CH ₃	Br
39	Cl	CN	Br	H	CH ₃	Br
40	Cl	CH ₃	CN	H	CH ₃	Br
41	Cl	F	CN	H	CH ₃	Br
42	Cl	Cl	CN	H	CH ₃	Br
43	Cl	Br	CN	H	CH ₃	Br
44	Cl	CN	CN	H	CH ₃	Br
45	H	CH ₃	Cl	H	-CH ₂ CH ₃	Br
46	H	Cl	Cl	H	-CH ₂ CH ₃	Br
47	H	CH ₃	CN	H	-CH ₂ CH ₃	Br
48	H	Cl	CN	H	-CH ₂ CH ₃	Br
49	Cl	CH ₃	Cl	H	-CH ₂ CH ₃	Br
50	Cl	Cl	Cl	H	-CH ₂ CH ₃	Br
51	Cl	CH ₃	CN	H	-CH ₂ CH ₃	Br
52	Cl	Cl	CN	H	-CH ₂ CH ₃	Br
53	H	CH ₃	F	H	-CH(CH ₃) ₂	Br
54	H	Cl	F	H	-CH(CH ₃) ₂	Br
55	H	CH ₃	Cl	H	-CH(CH ₃) ₂	Br
56	H	Cl	Cl	H	-CH(CH ₃) ₂	Br
57	H	Br	Cl	H	-CH(CH ₃) ₂	Br
58	H	CH ₃	Br	H	-CH(CH ₃) ₂	Br
59	H	Cl	Br	H	-CH(CH ₃) ₂	Br
60	H	Br	Br	H	-CH(CH ₃) ₂	Br
61	H	CH ₃	CN	H	-CH(CH ₃) ₂	Br
62	H	Cl	CN	H	-CH(CH ₃) ₂	Br
63	H	Br	CN	H	-CH(CH ₃) ₂	Br
64	Cl	CH ₃	F	H	-CH(CH ₃) ₂	Br
65	Cl	Cl	F	H	-CH(CH ₃) ₂	Br
66	Cl	CH ₃	Cl	H	-CH(CH ₃) ₂	Br
67	Cl	Cl	Cl	H	-CH(CH ₃) ₂	Br
68	Cl	Br	Cl	H	-CH(CH ₃) ₂	Br
69	Cl	CH ₃	Br	H	-CH(CH ₃) ₂	Br
70	Cl	Cl	Br	H	-CH(CH ₃) ₂	Br
71	Cl	Br	Br	H	-CH(CH ₃) ₂	Br
72	Cl	CH ₃	CN	H	-CH(CH ₃) ₂	Br
73	Cl	Cl	CN	H	-CH(CH ₃) ₂	Br
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75	H	CH ₃	Cl	H		Br

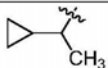
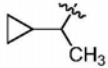
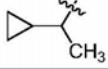
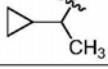
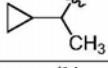
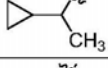
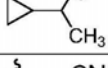
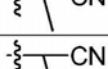
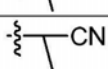
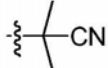
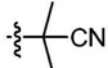
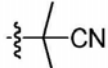
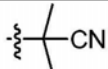
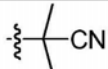
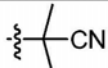
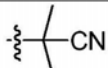
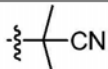
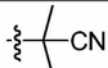
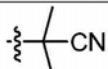
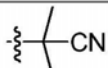
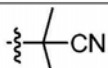
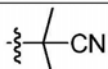
[0069]

76	H	Cl	Cl	H		Br
77	H	Br	Cl	H		Br
78	H	CH ₃	Br	H		Br
79	H	Cl	Br	H		Br
80	H	CH ₃	CN	H		Br
81	H	Cl	CN	H		Br
82	Cl	CH ₃	Cl	H		Br
83	Cl	Cl	Cl	H		Br
84	Cl	CH ₃	CN	H		Br
85	Cl	Cl	CN	H		Br
86	H	CH ₃	Cl	H		Br
87	H	Cl	Cl	H		Br
88	H	Br	Cl	H		Br
89	H	CH ₃	Br	H		Br
90	H	Cl	Br	H		Br
91	H	CH ₃	CN	H		Br
92	H	Cl	CN	H		Br
93	Cl	CH ₃	Cl	H		Br
94	Cl	Cl	Cl	H		Br
95	Cl	CH ₃	CN	H		Br
96	Cl	Cl	CN	H		Br
97	H	CH ₃	Cl	H		Br
98	H	Cl	Cl	H		Br
99	H	CH ₃	F	H		Br
100	H	Cl	F	H		Br
101	H	CH ₃	Cl	H		Br

[0070]

102	H	F	Cl	H		Br
103	H	Cl	Cl	H		Br
104	H	Br	Cl	H		Br
105	H	CN	Cl	H		Br
106	H	CH ₃	Br	H		Br
107	H	F	Br	H		Br
108	H	Cl	Br	H		Br
109	H	Br	Br	H		Br
110	H	CN	Br	H		Br
111	H	CH ₃	CN	H		Br
112	H	F	CN	H		Br
113	H	Cl	CN	H		Br
114	H	CN	CN	H		Br
115	H	Br	CN	H		Br
116	Cl	CH ₃	F	H		Br
117	Cl	Cl	F	H		Br
118	Cl	CH ₃	Cl	H		Br
119	Cl	F	Cl	H		Br
120	Cl	Cl	Cl	H		Br
121	Cl	Br	Cl	H		Br
122	Cl	CN	Cl	H		Br
123	Cl	CH ₃	Br	H		Br
124	Cl	F	Br	H		Br

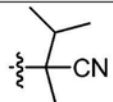
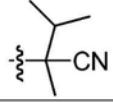
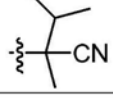
[0071]

125	Cl	Cl	Br	H		Br
126	Cl	Br	Br	H		Br
127	Cl	CN	Br	H		Br
128	Cl	CH ₃	CN	H		Br
129	Cl	F	CN	H		Br
130	Cl	Cl	CN	H		Br
131	Cl	CN	CN	H		Br
132	H	CH ₃	Cl	H		Br
133	H	Cl	Cl	H		Br
134	H	Cl	Br	H		Br
135	H	CH ₃	F	H		Br
136	H	Cl	F	H		Br
137	H	CH ₃	Cl	H		Br
138	H	F	Cl	H		Br
139	H	Cl	Cl	H		Br
140	H	Br	Cl	H		Br
141	H	CN	Cl	H		Br
142	H	CH ₃	Br	H		Br
143	H	F	Br	H		Br
144	H	Cl	Br	H		Br
145	H	Br	Br	H		Br
146	H	CN	Br	H		Br
147	H	CH ₃	CN	H		Br

[0072]

148	H	F	CN	H		Br
149	H	Cl	CN	H		Br
150	H	CN	CN	H		Br
151	H	Br	CN	H		Br
152	Cl	CH ₃	F	H		Br
153	Cl	Cl	F	H		Br
154	Cl	CH ₃	Cl	H		Br
155	Cl	F	Cl	H		Br
156	Cl	Cl	Cl	H		Br
157	Cl	Br	Cl	H		Br
158	Cl	CN	Cl	H		Br
159	Cl	CH ₃	Br	H		Br
160	Cl	F	Br	H		Br
161	Cl	Cl	Br	H		Br
162	Cl	Br	Br	H		Br
163	Cl	CN	Br	H		Br
164	Cl	CH ₃	CN	H		Br
165	Cl	F	CN	H		Br
166	Cl	Cl	CN	H		Br
167	Cl	CN	CN	H		Br
168	Cl	Br	CN	H		Br

[0073]

169	H	CH ₃	Cl	H		Br
170	H	Cl	Cl	H		Br
171	H	Cl	Br	H		Br
172	H	CH ₃	Cl	H		Br
173	H	Cl	Cl	H		Br
174	H	CH ₃	Cl	CH ₃	CH ₃	Br
175	H	Cl	Cl	CH ₃	CH ₃	Br
176	H	CH ₃	Br	CH ₃	CH ₃	Br
177	H	Cl	Br	CH ₃	CH ₃	Br
178	H	CH ₃	CN	CH ₃	CH ₃	Br
179	H	Cl	CN	CH ₃	CH ₃	Br
180	Cl	CH ₃	Cl	CH ₃	CH ₃	Br
181	Cl	Cl	Cl	CH ₃	CH ₃	Br
182	Cl	CH ₃	Br	CH ₃	CH ₃	Br
183	Cl	Cl	Br	CH ₃	CH ₃	Br
184	Cl	CH ₃	CN	CH ₃	CH ₃	Br
185	Cl	Cl	CN	CH ₃	CH ₃	Br
186	H	CH ₃	Cl	H	H	Cl
187	H	Cl	Cl	H	H	Cl
188	H	CH ₃	Br	H	H	Cl
189	H	Cl	Br	H	H	Cl
190	Cl	CH ₃	F	H	H	Cl
191	Cl	Cl	F	H	H	Cl
192	Cl	CH ₃	Cl	H	H	Cl
193	Cl	Cl	Cl	H	H	Cl
194	Cl	CH ₃	Br	H	H	Cl
195	Cl	Cl	Br	H	H	Cl
196	H	CH ₃	F	H	CH ₃	Cl
197	H	Cl	F	H	CH ₃	Cl
198	H	CH ₃	Cl	H	CH ₃	Cl
199	H	F	Cl	H	CH ₃	Cl
200	H	Cl	Cl	H	CH ₃	Cl
201	H	Br	Cl	H	CH ₃	Cl
202	H	CN	Cl	H	CH ₃	Cl
203	H	CH ₃	Br	H	CH ₃	Cl
204	H	F	Br	H	CH ₃	Cl
205	H	Cl	Br	H	CH ₃	Cl
206	H	Br	Br	H	CH ₃	Cl

[0074]

207	H	CN	Br	H	CH ₃	Cl
208	H	CH ₃	CN	H	CH ₃	Cl
209	H	F	CN	H	CH ₃	Cl
210	H	Cl	CN	H	CH ₃	Cl
211	H	CN	CN	H	CH ₃	Cl
212	H	Br	CN	H	CH ₃	Cl
213	Cl	CH ₃	F	H	CH ₃	Cl
214	Cl	Cl	F	H	CH ₃	Cl
215	Cl	CH ₃	Cl	H	CH ₃	Cl
216	Cl	F	Cl	H	CH ₃	Cl
217	Cl	Cl	Cl	H	CH ₃	Cl
218	Cl	Br	Cl	H	CH ₃	Cl
219	Cl	CN	Cl	H	CH ₃	Cl
220	Cl	CH ₃	Br	H	CH ₃	Cl
221	Cl	F	Br	H	CH ₃	Cl
222	Cl	Cl	Br	H	CH ₃	Cl
223	Cl	Br	Br	H	CH ₃	Cl
224	Cl	CN	Br	H	CH ₃	Cl
225	Cl	CH ₃	CN	H	CH ₃	Cl
226	Cl	F	CN	H	CH ₃	Cl
227	Cl	Cl	CN	H	CH ₃	Cl
228	Cl	Br	CN	H	CH ₃	Cl
229	Cl	CN	CN	H	CH ₃	Cl
230	H	CH ₃	Cl	H	-CH ₂ CH ₃	Cl
231	H	Cl	Cl	H	-CH ₂ CH ₃	Cl
232	H	CH ₃	CN	H	-CH ₂ CH ₃	Cl
233	H	Cl	CN	H	-CH ₂ CH ₃	Cl
234	Cl	CH ₃	Cl	H	-CH ₂ CH ₃	Cl
235	Cl	Cl	Cl	H	-CH ₂ CH ₃	Cl
236	Cl	CH ₃	CN	H	-CH ₂ CH ₃	Cl
237	Cl	Cl	CN	H	-CH ₂ CH ₃	Cl
238	H	CH ₃	F	H	-CH(CH ₃) ₂	Cl
239	H	Cl	F	H	-CH(CH ₃) ₂	Cl
240	H	CH ₃	Cl	H	-CH(CH ₃) ₂	Cl
241	H	Cl	Cl	H	-CH(CH ₃) ₂	Cl
242	H	Br	Cl	H	-CH(CH ₃) ₂	Cl
243	H	CH ₃	Br	H	-CH(CH ₃) ₂	Cl
244	H	Cl	Br	H	-CH(CH ₃) ₂	Cl
245	H	Br	Br	H	-CH(CH ₃) ₂	Cl
246	H	CH ₃	CN	H	-CH(CH ₃) ₂	Cl
247	H	Cl	CN	H	-CH(CH ₃) ₂	Cl
248	H	Br	CN	H	-CH(CH ₃) ₂	Cl
249	Cl	CH ₃	F	H	-CH(CH ₃) ₂	Cl

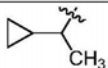
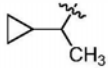
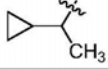
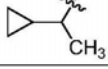
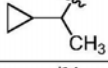
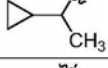
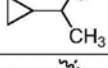
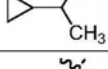
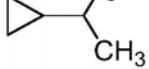
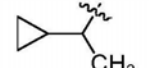
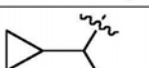
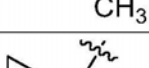
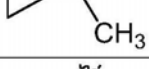
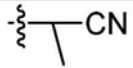
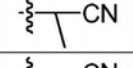
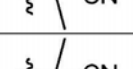
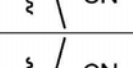
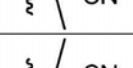
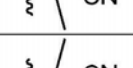
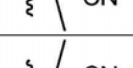
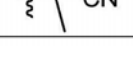
[0075]

250	Cl	Cl	F	H	$-\text{CH}(\text{CH}_3)_2$	Cl
251	Cl	CH_3	Cl	H	$-\text{CH}(\text{CH}_3)_2$	Cl
252	Cl	Cl	Cl	H	$-\text{CH}(\text{CH}_3)_2$	Cl
253	Cl	Br	Cl	H	$-\text{CH}(\text{CH}_3)_2$	Cl
254	Cl	CH_3	Br	H	$-\text{CH}(\text{CH}_3)_2$	Cl
255	Cl	Cl	Br	H	$-\text{CH}(\text{CH}_3)_2$	Cl
256	Cl	Br	Br	H	$-\text{CH}(\text{CH}_3)_2$	Cl
257	Cl	CH_3	CN	H	$-\text{CH}(\text{CH}_3)_2$	Cl
258	Cl	Cl	CN	H	$-\text{CH}(\text{CH}_3)_2$	Cl
259	Cl	Br	CN	H	$-\text{CH}(\text{CH}_3)_2$	Cl
260	H	CH_3	Cl	H		Cl
261	H	Cl	Cl	H		Cl
262	H	Br	Cl	H		Cl
263	H	CH_3	Br	H		Cl
264	H	Cl	Br	H		Cl
265	H	CH_3	CN	H		Cl
266	H	Cl	CN	H		Cl
267	Cl	CH_3	Cl	H		Cl
268	Cl	Cl	Cl	H		Cl
269	Cl	CH_3	CN	H		Cl
270	Cl	Cl	CN	H		Cl
271	H	CH_3	Cl	H		Cl
272	H	Cl	Cl	H		Cl
273	H	Br	Cl	H		Cl
274	H	CH_3	Br	H		Cl
275	H	Cl	Br	H		Cl
276	H	CH_3	CN	H		Cl
277	H	Cl	CN	H		Cl
278	Cl	CH_3	Cl	H		Cl
279	Cl	Cl	Cl	H		Cl
280	Cl	CH_3	CN	H		Cl

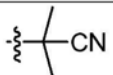
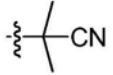
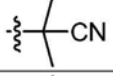
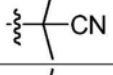
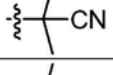
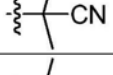
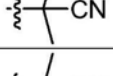
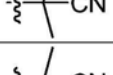
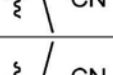
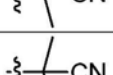
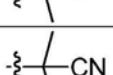
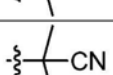
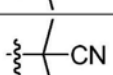
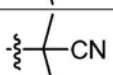
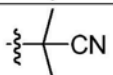
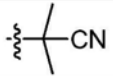
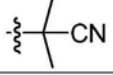
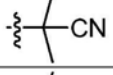
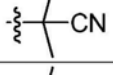
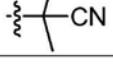
[0076]

281	Cl	Cl	CN	H		Cl
282	H	CH ₃	Cl	H		Cl
283	H	Cl	Cl	H		Cl
284	H	CH ₃	F	H		Cl
285	H	Cl	F	H		Cl
286	H	CH ₃	Cl	H		Cl
287	H	F	Cl	H		Cl
288	H	Cl	Cl	H		Cl
289	H	Br	Cl	H		Cl
290	H	CN	Cl	H		Cl
291	H	CH ₃	Br	H		Cl
292	H	F	Br	H		Cl
293	H	Cl	Br	H		Cl
294	H	Br	Br	H		Cl
295	H	CN	Br	H		Cl
296	H	CH ₃	CN	H		Cl
297	H	F	CN	H		Cl
298	H	Cl	CN	H		Cl
299	H	CN	CN	H		Cl
300	H	Br	CN	H		Cl
301	Cl	CH ₃	F	H		Cl
302	Cl	Cl	F	H		Cl
303	Cl	CH ₃	Cl	H		Cl

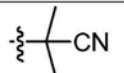
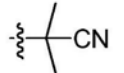
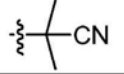
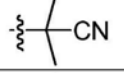
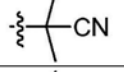
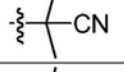
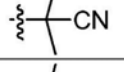
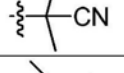
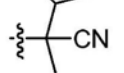
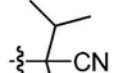
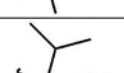
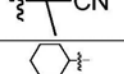
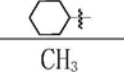
[0077]

304	Cl	F	Cl	H		Cl
305	Cl	Cl	Cl	H		Cl
306	Cl	Br	Cl	H		Cl
307	Cl	CN	Cl	H		Cl
308	Cl	CH ₃	Br	H		Cl
309	Cl	F	Br	H		Cl
310	Cl	Cl	Br	H		Cl
311	Cl	Br	Br	H		Cl
312	Cl	CN	Br	H		Cl
313	Cl	CH ₃	CN	H		Cl
314	Cl	F	CN	H		Cl
315	Cl	Cl	CN	H		Cl
316	Cl	CN	CN	H		Cl
317	H	CH ₃	Cl	H		Cl
318	H	Cl	Cl	H		Cl
319	H	Cl	Br	H		Cl
320	H	CH ₃	F	H		Cl
321	H	Cl	F	H		Cl
322	H	CH ₃	Cl	H		Cl
323	H	F	Cl	H		Cl
324	H	Cl	Cl	H		Cl

[0078]

325	H	Br	Cl	H		Cl
326	H	CN	Cl	H		Cl
327	H	CH ₃	Br	H		Cl
328	H	F	Br	H		Cl
329	H	Cl	Br	H		Cl
330	H	Br	Br	H		Cl
331	H	CN	Br	H		Cl
332	H	CH ₃	CN	H		Cl
333	H	F	CN	H		Cl
334	H	Cl	CN	H		Cl
335	H	CN	CN	H		Cl
336	H	Br	CN	H		Cl
337	Cl	CH ₃	F	H		Cl
338	Cl	Cl	F	H		Cl
339	Cl	CH ₃	Cl	H		Cl
340	Cl	F	Cl	H		Cl
341	Cl	Cl	Cl	H		Cl
342	Cl	Br	Cl	H		Cl
343	Cl	CN	Cl	H		Cl
344	Cl	CH ₃	Br	H		Cl
345	Cl	F	Br	H		Cl

[0079]

346	Cl	Cl	Br	H		Cl
347	Cl	Br	Br	H		Cl
348	Cl	CN	Br	H		Cl
349	Cl	CH3	CN	H		Cl
350	Cl	F	CN	H		Cl
351	Cl	Cl	CN	H		Cl
352	Cl	CN	CN	H		Cl
353	Cl	Br	CN	H		Cl
354	H	CH3	Cl	H		Cl
355	H	Cl	Cl	H		Cl
356	H	Cl	Br	H		Cl
357	H	CH3	Cl	H		Cl
358	H	Cl	Cl	H		Cl
359	H	CH3	Cl	CH3	CH3	Cl
360	H	Cl	Cl	CH3	CH3	Cl
361	H	CH3	Br	CH3	CH3	Cl
362	H	Cl	Br	CH3	CH3	Cl
363	H	CH3	CN	CH3	CH3	Cl
364	H	Cl	CN	CH3	CH3	Cl
365	Cl	CH3	Cl	CH3	CH3	Cl
366	Cl	Cl	Cl	CH3	CH3	Cl
367	Cl	CH3	Br	CH3	CH3	Cl
368	Cl	Cl	Br	CH3	CH3	Cl
369	Cl	CH3	CN	CH3	CH3	Cl
370	Cl	Cl	CN	CH3	CH3	Cl